Conferences and Reviews

Biology and Treatment of Adult Acute Lymphoblastic Leukemia

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The molecular analysis of acute lymphoblastic leukemia (ALL) has provided exciting insights into the pathogenesis of this disease. This disease is heterogenous and can be subtyped based on chromosomal, immunophenotypic, and structural criteria. The varying prognostic implications of different ALL subtypes markedly influence the treatment decisions in adults. Many patients with T-cell ALL can be cured with chemotherapy alone. In contrast, patients with early B-lineage ALL with certain chromosomal abnormalities, especially the Philadelphia chromosome, do not have durable responses to chemotherapy and should receive a bone marrow transplantation if an HLA-matched donor is available. Recent reports have shown improved results for adults with B-cell ALL (Burkitt's) after intensive alternating cycles of chemotherapy containing high doses of methotrexate and cyclophosphamide. Future clinical and laboratory investigation should lead to the development of novel and possibly more effective treatments specifically tailored for different subsets of ALL.

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A large amount of information has recently accrued regarding both the biology and the treatment of acute lymphoblastic leukemia (ALL). The molecular analysis of lymphoblasts has provided exciting new information about oncogenesis and the control of cellular proliferation. Intensive regimens of chemotherapy have resulted in cure for a sizable number of patients. New information is available concerning the role of both allogeneic and autologous marrow transplantation in the management of patients with this disease. In this review, we will consider recent advances in the understanding and management of adult ALL.*

Classification

Morphologic Features

Morphologic and immunophenotypic features have traditionally been used to classify patients with ALL. The French-American-British classification recognizes three structural subtypes: L1, L2, and L3.[1] The L1 subtype consists of small uniform lymphoblasts and is found in 25% to 30% of cases of adult ALL. The L2 subtype consists of larger pleomorphic lymphoblasts and is the most common structural subtype found in adults (65% to 70% of cases). The L3 subtype, whose structure resembles that of Burkitt's lymphoma, is usually found in patients with B-cell ALL whose blasts express surface membrane immunoglobulin. The L3 subtype is found infrequently in adults with ALL (2% to 7%).

Immunophenotyping

Monoclonal antibodies and the molecular analysis of surface-receptor gene rearrangements can now be used to more precisely define lineage-specific features of leukemic lymphoblasts.[2,3] Acute lymphoblastic leukemia cells undergo rearrangements of immunoglobulin and T cell-receptor genes and express epitopes of antigen-receptor molecules and differentiation-associated surface glycoproteins in a manner that approximates the events of normal B- and T-lymphocyte development.

B-lineage ALL can be subdivided into at least four subtypes (Table 1). In early pre-B ALL, the lymphoblasts express one or more B lineage-specific surface antigens, but do not have surface or cytoplasmic immunoglobulins. Early pre-B ALL is further divided into two subtypes based on the presence or absence of the common ALL antigen (CD10, or CALLA). The CD10 antigen has recently been identified as a neutral endopeptidase.[4] Early pre-B ALL that is CALLA-positive is the most frequent immunologic subtype in adults with ALL (50% to 60%). Lymphoblasts in this subtype express one or more B lineage-specific antigens (CD19, CD20, and CD22) and usually contain high levels of the enzyme terminal deoxynucleotidyl transferase (TdT).

Early pre-B ALL that is CALLA-negative is found in 10% to 38% of adult patients with ALL.[5-10] In the past,

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ABBREVIATIONS USED IN TEXT

ALL = acute lymphoblastic leukemia
BCR = break-point cluster region
CALGB = Cancer and Leukemia Group B [trial]
CALLA = common ALL antigen
CDR-III = complementarity-determining region III
CML = chronic myeloid leukemia
CNS = central nervous system
PCR = polymerase chain reaction
Ph = Philadelphia chromosome
TdT = terminal deoxynucleotidyl transferase

this subtype was labeled null-cell ALL because it expressed neither CD10 nor T lineage-specific surface antigens. With the use of several monoclonal antibodies for early B-lineage surface antigens and molecular analysis for the detection of immunoglobulin gene rearrangements, it is now known that most null-cell blasts are derived from B precursor cells and are a more immature subset than CALLA-positive early pre-B ALL.[11] Early pre-B ALL blasts that are CALLA-negative usually express CD19 and TdT and have rearranged immunoglobulin genes. Immunoglobulin heavy-chain gene rearrangements should not be considered lineage specific because they can be seen in about 15% of patients with T-cell ALL.[12]

Lymphoblasts in the pre-B ALL subtype express B lineage-specific antigens, TdT, and cytoplasmic immunoglobulin heavy chains, but do not express surface immunoglobulin. A specific chromosomal translocation, t(1:19), is found in about a fourth of pre-B cases and is associated with a poor prognosis.[13,14] Little information is available on this immunophenotype in adults with ALL.

B-cell ALL is uncommon in adults (2% to 7%).[5-10] It shares many cytogenetic, immunologic, cytologic, and clinical features with Burkitt's lymphoma.[15] The Burkitt's lymphoblasts often have a distinctive structure characterized by deeply basophilic cytoplasm that contains prominent vacuoles (L3). CD10 may be present on the surface of these cells, although TdT is not usually expressed. Kinetic studies indicate a rapid proliferative potential with in vitro doubling times as short as 26 hours.

About 25% of adults with ALL have T-lineage disease (Table 1).[5-10] T-cell ALL blasts express the prothymocyte antigen CD7 and often additional early or intermediate thymocyte antigens, including CD5, CD2, CD4, and CD8. In 5% to 40% of cases, T-cell ALL blasts express CD10 in combination with other T-cell antigens. T-cell ALL blasts contain TdT and, in most instances, one or more of the T cell-receptor genes are rearranged.[3] Pre–T-cell ALL blasts constitute a more immature T-lineage phenotype and express only surface CD7 and often cytoplasmic CD3 determinants.[10]

Acute mixed-lineage leukemias concurrently express lymphoid as well as myeloid surface antigens. These leukemias are called biphenotypic if they consist of individual blast cells expressing both myeloid (CD13, CD14, or CD33) and lymphoid antigens. Bilineage leukemias consist of two populations of blast cells that express either lymphoid or myeloid antigens.[16] With more detailed immunophenotypic analysis, the incidence of mixed-lineage leukemias appears to be increasing. Overall, myeloid coexpression is found in 10% to 20% of adults with ALL and is seen more often in CALLA-negative early pre-B ALL or pre-T ALL and in patients with unique chromosomal translocations.[17] Recently described assays using monoclonal antibodies to detect the early expression of cytoplasmic proteins such as myeloperoxidase, CD3, CD22, and CD33 may more accurately characterize acute mixed-lineage leukemias.[18] More stringent diagnostic criteria may further enhance the clinical usefulness of this ALL subtype.

Cytogenetic and Molecular Anomalies

Cytogenetic abnormalities are common in patients with ALL and are one of the most important independent prognostic variables for predicting outcome.[19] Recent studies indicate that it may be possible to identify the clonal chromosomal abnormalities in more than 90% of cases of ALL.[20] These chromosomal anomalies may aid in the diagnosis by showing the specific karyotype and often correlate with other clinical features of the disease.

Abnormalities of Cell Ploidy

The distribution of chromosomal ploidy anomalies in

TABLE 1.—*Immunologic Classification of B- and T-Lineage Acute Lymphoblastic Leukemia*

	CD Determinants and Cell Markers					
Classification	*CD19*	*CD10 (CALLA)*	*CD20*	*CytIg*	*SurfIg*	*TdT*
Early pre-B						
CALLA-negative	+	−	−	−	−	+
CALLA-positive	+	+	±	−	−	+
Pre-B cell	+	±	+	+	−	+
B cell	+	±	+	−	+	−
	CD7	*CD5*	*CD2*	*CD1*	*CD4*	*CD8*	*TdT*
Pre-T cell	+	+	±	−	−	−	+
T cell	+	+	+	+	+	+	+

CALLA = common acute lymphoblastic leukemia antigen, CytIg = cytoplasmic immunoglobulin, SurfIg = surface membrane immunoglobulin, TdT = terminal deoxynucleotidyl transferase, + = present, − = absent, ± = may or may not be present

adult ALL is as follows: normal, 15% to 20%; hyperdiploid (>50), 10% to 20%; hyperdiploid (47 to 50), 10%; pseudodiploid (46, abnormal), 30% to 50%; and hypodiploid, 5% to 8%.[21] Patients with hyperdiploid karyotypes appear to have a relatively favorable prognosis, whereas patients with pseudodiploid karyotypes usually have one of several specific chromosomal translocations and have a particularly poor prognosis.[22]

Phenotype-Specific Chromosomal Translocations

The most common chromosomal translocations found in adult patients with ALL include t(9;22)(q34;q11), t(8;14)(q24;q32), t(4;11)(q21;q23), t(1;19)(q23;p13), and translocations with break points near the α-chain locus of the T-cell receptor at 14q11 or near the β-chain locus of the T-cell receptor at 7q35 (Tables 2 and 3).[19,22]

The t(9;22)(q34;q11) translocation, or Philadelphia chromosome (Ph), is found by traditional cytogenetic analysis in about 20% of adults with ALL.[19] Patients with this translocation often fail to achieve remission or have early relapse of their disease. In both chronic myeloid leukemia (CML) and ALL, the c-*abl* gene is translocated from chromosome 9 to chromosome 22.[23] Break points are scattered over more than 175 kilobases (kb) upstream of *abl* exon II. In contrast, breaks on chromosome 22 occur within two limited areas, called the major and minor break-point cluster regions (BCRs).[23] The break points in CML map almost entirely to the major BCR, whereas both the major and minor BCRs appear to be involved in Ph-positive ALL. As a consequence of the translocation, a *BCR-abl* fusion gene is produced that consists of upstream sequences from *BCR* and downstream sequences from *abl*. *BCR-abl* fusion genes with the major BCR break point are transcribed into a chimeric 8.5-kb messenger RNA and produce a p210 *BCR-abl* protein. The *BCR-abl* fusion genes with the minor BCR break point express a chimeric 7.0-kb messenger RNA and a p190 fusion protein. Both fusion proteins exhibit deregulated tyrosine kinase activity.[24,25] Chronic myeloid leukemia has been induced in some transgenic mice expressing p210, and acute leukemia has been seen in some transgenic mice expressing p190.[26,27]

The polymerase chain reaction (PCR) has recently been used to look for *BCR-abl* rearrangements: *BCR-abl* transcripts were found in 43% of adults with ALL, but in only 6% of children with newly diagnosed ALL and 17% of children with relapsed ALL.[28] No rearrangements were found in patients with T-cell disease; 55% of adults with early pre–B-cell ALL were PCR-positive. Two thirds of PCR-positive adults expressed minor BCR break points, and a third expressed BCR break points within the major region. Positivity for PCR correlated with the height of the leukocyte count at presentation and with patient's age.

TABLE 2.—*Characteristic Chromosomal Translocations in Acute Lymphoblastic Leukemia—Translocations Generating Chimeric (Fusion) Proteins*

Translocation	Gene	Phenotype
t(9;22)(q34;q11).....	*BCR-abl*	Early pre-B cell
t(1;19)(q23;p13).....	*E2A-PBX1*	Pre-B cell
t(17;19)(q22;p13).....	*E2A-HLF*	Early pre-B cell
t(4;11)(q21;q23).....	*MLL-AF4*	Early pre-B cell, often with myeloid antigen coexpression
t(11;19)(q23;p13).....	*MLL-ENL*	

TABLE 3.—*Characteristic Chromosomal Translocations in Acute Lymphoblastic Leukemia—Translocations With Rearrangement of an Antigen-Receptor Locus*

Translocation	Gene	Antigen Receptor	Phenotype
t(8;14)(q24;q32).....	c-*myc*	Ig heavy chain	B cell
t(2;8)(p12;q24).....	c-*myc*	Ig κ light chain	B cell
t(8;22)(q24;q11).....	c-*myc*	Ig λ light chain	B cell
t(11;14)(p15;q11).....	*TTG1/RHOM1*	T α/δ locus	T cell
t(1;14)(p32;q11).....	*TAL1/SCL*	T α/δ locus	T cell
t(10;14)(q24;q11).....	*HOX11*	T α/δ locus	T cell
t(7;19)(q35;p13).....	*LYL1*	T β locus	T cell
t(7;9)(q35;q34).....	*TAL2*	T β locus	T cell
t(7;11)(q35;p13).....	*TTG2/RHOM2*	T β locus	T cell

Ig = immunoglobulin

The t(8;14)(q24;q32) translocation is found in patients with B-cell ALL. Variant translocations in B-cell leukemia include t(2;8)(p12;q24) and t(8;22)-(q24;q11).[29] As a consequence of the t(8;14) translocation, the c-*myc* proto-oncogene is transferred from chromosome 8 to the heavy-chain immunoglobulin locus adjacent to the coding sequences for the immunoglobulin constant region. In the variant translocations, c-*myc* remains on chromosome 8, and portions of either the κ (chromosome 2) or λ (chromosome 22) light-chain genes are translocated to regions just downstream of the c-*myc* locus. These translocations appear to disrupt c-*myc* regulation, possibly through repositioning of strong immunoglobulin enhancers adjacent to the c-*myc* locus or in conjunction with c-*myc* mutations that occur coincidentally with the translocation.[30,31] B-cell neoplasms have been induced in transgenic mice that possess c-*myc* driven by an immunoglobulin gene enhancer.[32] Activated c-*myc* is also capable of malignant transformation when it is transfected into human B lymphoblasts infected with the Epstein-Barr virus.[33] It is likely that other genetic anomalies are required for the malignant transformation of B cells in addition to the deregulation of c-*myc* expression.

The t(4;11)(q21;q23) translocation is found in about 5% of adults with ALL.[19,22] Leukemic blasts with this translocation usually have an early pre-B phenotype with rearranged immunoglobulin heavy-chain genes.[34] These cells can be induced to express monocytic features in vitro and can sometimes coexpress myeloid and lymphoid surface antigens in vivo, a characteristic of the mixed-lineage leukemias.[35] The chromosome 11q23 break point, which forms a reciprocal translocation with

chromosome 4 in t(4;11)(q21;q23), is also associated with the t(11;19)(q23;p13) translocation in ALL and is found in almost 10% of cases of acute myelogenous leukemia; the most common translocation seen in acute monocytic leukemia is t(9;11)(p22;q23).[36-38] The 11q23 break point is also seen in ALL patients in whom secondary acute myelogenous leukemia has developed.[39] This region likely contains one or more genes capable of modulating the commitment to lymphoid or myeloid differentiation. Recently, a gene—called *MLL* for mixed-lineage leukemia—was cloned from the 11q23 break point and was found to be a homologue of a *Drosophila trithorax* transcription factor.[40]

The t(1;19)(q23;p13) translocation is found in about 25% of patients with pre–B-cell ALL.[41] This translocation results in a rearrangement of upstream sequences from the *E2A* gene (which codes for a transcriptional regulator protein) on chromosome 19 with downstream sequences from the *PBX1* gene (which codes for a protein with a homeobox DNA-binding domain) on chromosome 1.[13,14] It is possible that the resultant fusion protein could initiate abnormal transcriptional regulation and play a role in leukemogenesis. Recently, the *E2A-PBX1* fusion product has been shown to induce lymphoid proliferation and lymphomas in transgenic mice.[42]

Translocations with break points near the α/δ locus of the T-cell receptor on chromosome 14 (band q11) or the β-chain T cell-receptor locus on chromosome 7 (band q35) have been seen in cases of acute T-cell ALL.[43,44] The t(11;14)(p15;q11) translocation results in a rearrangement of the T-cell receptor α/δ locus with a gene (*TTG1*) on chromosome 11 that codes for a possible DNA-binding zinc-finger transcriptional regulator protein.[45] In an alternative translocation, t(10;14)(q24;q11), the δ locus is rearranged with the *HOX11* proto-oncogene on chromosome 10.[46] The *TAL1* protein is another putative helix-loop-helix transcription factor identified at the translocation break point involving the T cell α/δ-receptor locus—t(1;14)(p32;q11).[47] The *TAL1* rearrangements may be found in as many as 25% of patients with T-cell ALL. The helix-loop-helix transcription factor genes *LYL1* and *TAL2* have been identified at break points involving the 7q35 T-cell β chain-receptor locus—t(7;19)(q35;p13) and t(7;9)(q35;q34), respectively.[44,48] Inversions of the long arm of chromosome 14 involving the α-chain locus at q11 and the immunoglobulin heavy-chain locus at q32 have also been seen in T-cell leukemia.[49]

Clinical Features

A third of adults with ALL present with infections, fever, or both, whereas a third will have hemorrhagic manifestations.[21] Lymphadenopathy and hepatosplenomegaly are seen at presentation in about half of adult patients. Mediastinal masses, sometimes accompanied by pleural effusions, have been reported in 15% of adults with ALL and are most commonly seen in patients with T-cell disease.[21] A few adults (4%) will present with signs or symptoms of central nervous system (CNS) involvement, including headache, vomiting, papilledema, lethargy, nuchal rigidity, or cranial nerve palsies (III, IV, VI, and VII). An additional 3% to 10% of adults will have asymptomatic CNS disease, usually diagnosed by surveillance lumbar puncture and the examination of cytocentrifuged cerebrospinal fluid.

Extramedullary disease in adult patients at other sites at presentation is infrequent. In contrast to children, adults rarely (1% to 2%) have bone or joint pain at diagnosis.[50] Clinical evidence of testicular involvement in adults at presentation is rare (<1%).[21] Isolated testicular relapses to date in adults have proved to be infrequent (1%) and do not warrant surveillance biopsies.[51]

Data on laboratory evaluation at presentation have recently been published following the analysis of two consecutive German multicenter trials involving 938 patients aged 15 to 65 years with ALL.[21] The leukocyte count is elevated ($>10 \times 10^9$ per liter [10,000 per mm^3]) in 59% of adults at presentation. Many adults (27%) will present with leukopenia (leukocyte count $<5 \times 10^9$ per liter [5,000 per mm^3]), and 25% will have an absolute neutrophil count of less than 500×10^6 per liter (500 per mm^3). Hyperleukocytosis (leukocyte count $>100 \times 10^9$ per liter) is found in 16% of adults at diagnosis. Careful examination of the peripheral smear will reveal circulating blasts in 92% of cases. A platelet count below 25×10^9 per liter is found in only 30% of adults at diagnosis, and 80% of adults will have a hemoglobin concentration of less than 120 grams per liter (<12 grams per dl). Recent data indicate that laboratory evidence of a consumptive coagulopathy is seen in 12% of patients before the initiation of chemotherapy and in 78% during remission induction therapy. Serious complications—pulmonary embolus, sagittal sinus thrombosis, hemorrhage—occurred in 34% of these patients.[52] Unusual laboratory manifestations of ALL include eosinophilia, bone marrow necrosis, and cyclic neutropenia.[53-55]

Two ALL immunologic subtypes have clinical features that are rather characteristic. T-cell ALL is frequently associated with high blood leukocyte counts (often more than 100×10^9 per liter), a mediastinal mass, and leptomeningeal leukemia at diagnosis. B-cell ALL is associated with extramedullary sites of disease in the abdomen or head and neck, as well as frequent CNS involvement. The tumor lysis syndrome with hyperuricemia, hyperkalemia, hyperphosphatemia, hypocalcemia, disseminated intravascular coagulation, and acute renal failure may accompany the onset of chemotherapy in B-cell ALL.[56]

Prognostic Factors

Data from several recent trials of adult ALL that used different intensive combination chemotherapy regimens have identified similar prognostic factors for remission duration. The most important of these factors appears to be cytogenetic abnormalities, time to achieve complete remission, initial leukocyte count, age, and immunolog-

TABLE 4.—*Adverse Prognostic Features in Acute Lymphoblastic Leukemia*

Indicator	*Unit*
Time to achieve complete remission, wk	>4
Cytogenetic abnormalities	t(9;22), t(4;11)
Leukocyte count, × 10^9/liter ($/mm^3$)	25-35 (25,000-35,000)
Age, yr	>35
Immunophenotype	Pre-T cell, CALLA-negative early pre-B cell
Mixed lineage	Myeloid antigen coexpression

ic subtype (Table 4).[5,17,19,51,57] In one study, patients at low risk without any of four adverse features—time to remission, >4 weeks; age, >35 years; leukocyte count, >30 × 10^9 per liter; and null-cell immunophenotype—were likely to have a continuous remission rate beyond five years of 62%. Patients with one or more of these adverse features had a predicted five-year relapse-free survival rate of 28%.[51] About 70% of adult ALL patients have one or more of the adverse prognostic factors listed in Table 4. Not all these prognostic factors are necessarily independent of each other. For example, the T-cell immunophenotype portends a good prognosis in adult ALL patients despite the fact that this phenotype is often associated with high leukocyte counts at presentation.

Time to Achieve Complete Remission

The time to achieve complete remission is inversely related to the remission duration. Obtaining complete remission within four or five weeks is associated with a substantially longer remission duration than when additional chemotherapy is required.[51,57] About 75% of adult patients currently achieve a complete remission with intensive chemotherapy; about 10% of these patients require more than four weeks of chemotherapy.

Cytogenetic Abnormalities

An abnormal karyotype (other than hyperdiploidy) is an adverse risk factor independent of other established prognostic factors.[19] The most frequently seen translocations in adult ALL—t(9;22)(q34;q11), t(4;11)(q21;-q23)—are associated with a somewhat lower incidence of complete remission and a markedly shorter remission duration.[19,22,28] In a Cancer and Leukemia Group B (CALGB) study, the presence of the *BCR-abl* gene was assessed in adults with ALL using the Southern blot test and pulsed-field gel analysis. Nearly a third (30%) of cases were positive for *BCR-abl*. Although rates of achieving complete remission were similar between *BCR-abl*–positive and –negative groups, there were more early relapses and a shorter remission duration in the *BCR-abl*–positive group.[58] The pronounced disparity in the incidence of the translocation t(9;22)(q34;q11) between children and adults—6% versus 43%, respectively, by PCR analysis—may explain much of the observed difference in survival between these two groups following chemotherapy.[28]

Leukocyte Count

Recent studies indicate that a peripheral leukocyte count at presentation of greater than 25 to 35 × 10^9 per liter is associated with a reduced remission duration in adult patients.[5,8,51] The leukocyte count does not appear to be an independent risk factor and correlates with both age and cytogenetic abnormalities.[28] Clinical leukostasis is rare in patients with ALL, even with leukocyte counts of greater than 100 × 10^9 per liter.

Age

Most studies indicate that increasing age is associated with a shorter remission duration. A recent large study that used intensive combination chemotherapy suggested that being older than 35 was associated with shorter remissions,[51] whereas another large study that used a different protocol of intensive chemotherapy found little difference in relapse rates between patients aged 15 to 25 and those aged 25 to 60; patients older than 60 years had substantially higher relapse rates.[5] In the French Group trial, 58 patients older than 50 were treated with chemotherapy; the three-year disease-free survival rate was 24%.[59] Although many studies do not indicate that age is correlated with rates of achieving remission in adult ALL, contradictory data exist, and when large numbers of patients are included, it appears that there is a continuous decline in complete remission rates with increasing age.[60] In one study, 82% of adults younger than 40 years obtained remission, whereas only 67% of patients 40 to 59 years of age achieved remission, and patients 60 years or older obtained remission only 45% of the time.[61] In a recent series of patients older than 60 with ALL, 22 patients were treated aggressively with curative intent; complete remissions were obtained in only 7 (32%).[62] The higher incidence of karyotypic anomalies and mixed-lineage (biphenotypic) leukemias in older adults may in part explain the worse prognosis in this subgroup of patients with ALL.[28,63]

Immunophenotype

Patients with CALLA-positive early pre–B-cell ALL have traditionally been considered to have the most favorable subtype with regard to remission duration. Recent studies that used intensive chemotherapy, however, suggest that T-cell ALL may now be associated with the most prolonged remission duration.[5,6,9,51,57] In one study, the probability of continuous remission at five years was 59% for adults with T-cell ALL versus 31% for patients with CALLA-positive early pre–B-cell ALL.[57] It is possible that the use of frequent doses of cytarabine with or without cyclophosphamide may in part explain the improved survival of patients with T-cell ALL. T lymphoblasts accumulate high levels of cytarabine triphosphate and exhibit high nucleoside transport activity.[64] Late relapses have been noted as long as five

to six years after achieving complete remission in patients with CALLA-positive ALL, whereas relapses in T-cell ALL usually occur by three years after achieving remission.[57] The CALLA-negative, early pre–B-cell ALL subtype has been associated with a lower five-year relapse-free survival (24%) than either T-cell ALL (55%) or CALLA-positive ALL (34%).[51] Pre–T-cell ALL also appears to show lower responses to treatment than standard T-cell ALL.[10]

Remission rates for adult B-cell ALL (Burkitt's) are only about 40%, and remission durations are often less than 6 to 12 months.[21,65] It is possible that regimens using high doses of cyclophosphamide and methotrexate can increase the likelihood of achieving complete remission and lengthen the duration of remission in adults with B-cell ALL. Recent data indicate that a small number of adults with B-cell ALL treated with frequent cyclic combinations containing such drugs have two- to three-year disease-free survival rates of about 60%.[66-68]

In several studies, adult patients with myeloid antigen expression in early pre–B-cell ALL have a substantially lower likelihood of achieving complete remission (29% to 50%) than those patients whose blasts do not coexpress myeloid antigens (71% to 83%).[17,63,69,70] A CALGB cooperative trial prospectively studied 76 adults with ALL and identified myeloid-lymphoid antigen coexpression in 33% of cases. No differences in response or survival were seen between myeloid-positive and -negative patients expressing T-cell antigens. Among patients expressing B-cell antigens, however, myeloid-positive patients had fewer complete remissions and shorter survival.[63] Three subsequent single-institution studies comprising 40 to 62 patients also indicate that myeloid coexpression is associated with a poorer complete remission rate and a shorter remission duration.[69-71] Not all studies have found a prognostic importance for myeloid antigen coexpression, however, and this subject remains controversial.[72]

Detection of Minimal Residual Disease

Traditional morphologic methods of detecting minimal residual leukemia have not been sufficiently sensitive to detect leukemic cells constituting less than 2% to 5% of bone marrow mononuclear cells. Immunophenotyping, DNA flow cytometry, cytogenetics, and leukemic colony assays have also shown limited sensitivity and specificity for detecting minimal residual leukemia.[73] A number of alternative methods have recently been used in efforts to detect very small numbers of residual leukemic cells in the marrow of ALL patients during clinical remission.

Immunoglobulin or T cell-receptor gene rearrangement analysis has permitted the detection of 1 leukemic cell in as few as 500 normal mononuclear nucleated cells in the bone marrow of patients with ALL.[74] The use of the PCR to amplify leukemia-specific chromosomal translocations has increased the sensitivity for detecting minimal residual disease by three to four orders of magnitude.[73] The high incidence of the *BCR-abl* rearrangement using PCR analysis in adults with ALL may, for example, prove useful for the assessment of residual disease in many patients with early pre–B-cell ALL. The PCR has recently been used to assess *BCR-abl* minimal residual disease following marrow transplantation in patients with Ph-positive ALL. The detection of the *BCR-abl* transcripts by PCR preceded clinical relapse by three to nine weeks in eight patients; seven other patients have remained in remission with no evidence of minimal residual disease by PCR.[75] These results differ from those in patients with CML, in whom persistent *BCR-abl* transcripts are not always a sign of clinical relapse.[76] Many leukemia-specific chromosomal translocations have yet to be molecularly characterized, thus limiting the routine application of this method.

An alternative, albeit technically demanding, approach uses the clonal expansion of unique DNA sequences (the hypervariable complementarity-determining region III [CDR-III] of the immunoglobulin heavy chain) in B cell-lineage lymphoblasts.[77] Rearrangements of these sequences can be used as markers of the leukemic clone. In this method, PCR is used to amplify unique CDR-III sequences in leukemic blasts using primers that are homologous to consensus sequences in regions that flank the rearranged segment in the heavy-chain locus. The leukemia-specific CDR-III–amplified segments are then sequenced and used to generate diagnostic oligonucleotide probes.[77] This method, which is potentially applicable to most instances of B-lineage ALL, can detect 1 leukemic cell in a population of 100,000 normal cells. CDR-III–based PCR amplification has been used to assess minimal residual disease in a group of 181 patients with ALL.[78] The detection of disease by this clone-specific technique appeared to correlate with clinical outcome, and the extent of residual disease was related to the probability of relapse. Analogous clone-specific probes have also been generated for PCR in cases of T-cell ALL.[79] The main limitations of these techniques include the need to generate sequence-specific probes and the possibility that target gene rearrangements may be unstable during clonal evolution. It is likely that the adequacy and duration of ALL treatment, however, will in the future be determined in part by careful and sensitive assessments of minimal residual disease.

Treatment

Chemotherapy

Induction. The remission rate achieved in adults with the use of vincristine and prednisone alone is only 40% to 60%, and the use of this regimen has been associated with short remission durations despite the use of varied consolidation and maintenance regimens.[80] In a retrospective study from the Netherlands, administering vincristine and prednisone alone resulted in a complete remission rate of 46%, whereas the use of vincristine and prednisone plus daunorubicin achieved a complete remission rate of 68%.[81] A prospective, randomized

study by CALGB showed a complete remission rate of 47% (25/52) in adults given induction therapy with vincristine, prednisone, and asparaginase, whereas a regimen that used the same three medications plus daunorubicin resulted in a complete remission rate of 83% (38/46).[82] Remission rates of at least 70% to 80% have been achieved in most recent series of adult ALL using vincristine, prednisone, and an anthracycline with or without asparaginase.[21]

The use of high-dose cytarabine in combination with an induction regimen of vincristine, prednisone, and doxorubicin in de novo ALL does not result in a complete remission rate superior to that achieved with conventional treatment.[83] Similarly, administering either high-dose cytarabine alone or an anthracycline plus standard-dose cytarabine does not appear to result in better overall survival rates than conventional induction regimens in de novo ALL.[83-85] Such an approach may prove beneficial, however, in subsets of high-risk patients with ALL.

B-cell ALL does not respond well to conventional ALL induction regimens.[65] A different induction regimen using alternating cycles of high-dose cyclophosphamide, methotrexate, and cytarabine is recommended for patients with this subtype of ALL.[66-68]

Central nervous system therapy. Leukemic involvement of the CNS is present at diagnosis in about 10% of adults with ALL.[6,7,9] Risk factors for CNS disease include T-cell disease, Burkitt's leukemia, and an elevated leukocyte count ($>50 \times 10^9$ per liter).[86] The treatment of documented CNS disease usually consists of the intrathecal administration of methotrexate in combination with cranial irradiation.[87] Some investigators recommend placing an Ommaya reservoir to administer chemotherapy intraventricularly, although no studies have provided definitive support for this approach.[88] With adequate treatment, the presence of CNS leukemia at diagnosis does not appear to adversely influence relapse-free survival rates in adult patients with ALL.[51,57]

The incidence of CNS leukemic relapse at one year was 21% in a series of adults with ALL who received intensive chemotherapy without CNS prophylaxis.[86] In a randomized trial of cranial irradiation plus intrathecal methotrexate, the incidence of CNS relapse was reduced from 32% to 11% and the predicted two-year CNS relapse rate from 42% to 19%.[89] No difference was found between the two groups in hematologic remission duration or survival, however. The standard approach to CNS prophylaxis is to use intrathecal methotrexate plus cranial irradiation.[87] Alternative approaches—such as high systemic doses of cytarabine or methotrexate—do not appear to be superior to the combined use of intrathecal methotrexate plus cranial irradiation and may be associated with enhanced neurotoxicity, particularly in older patients.[81,90] Minimal neuropsychological toxicity has been reported in adults following CNS prophylaxis with intrathecal methotrexate plus cranial irradiation.[91] It seems reasonable to administer CNS prophylaxis to adults after achieving a complete remission, with the understanding that its role remains to be precisely defined and that the full effects of CNS prophylaxis may not be apparent in adults with ALL until its use is assessed in the context of more effective systemic therapy.

Continuation (postremission) chemotherapy. Consolidation or intensification chemotherapy refers to early treatment after obtaining remission with combinations of drugs of comparable intensity to induction chemotherapy, usually given in repeated courses over several months. Maintenance therapy refers to lower-dose treatment, usually given continuously for several years. Two small randomized studies support the use of consolidation or intensification therapy in adults with ALL. A French study randomly assigned 61 patients in remission to receive or not receive intensification therapy with doxorubicin, cytarabine, and asparaginase, administered monthly for three cycles. Disease-free survival at three years favored those patients receiving intensification, 38% versus 0%.[92] A European Organization for the Treatment of Cancer (EORTC) study randomly assigned 65 ALL patients in remission to receive either four months of intensive consolidation or one month of less intensive treatment: the median duration of complete remission favored those patients receiving the more intensive consolidation regimen, 45 versus 24 months.[93] A recent randomized CALGB study, however, failed to demonstrate benefit for two daunorubicin-plus-cytarabine consolidation cycles compared with the use of mercaptopurine plus methotrexate only.[94]

A number of uncontrolled studies using intensive consolidation regimens support the use of aggressive postremission chemotherapy in adults with ALL. The Memorial Sloan-Kettering Cancer Center (New York, NY; protocols L2 through L17M) has reported complete remission in 82% of 199 adults (median age, 25) and a disease-free survival rate at ten years of 38%.[6] A German multicenter study of 368 patients (median age, 25) achieved a remission rate of 74% and a ten-year disease-free survival rate of 35%.[95] A Stanford–University of California, San Francisco–City of Hope (Duarte, California) study of 109 adults (median age, 25) reported an 88% remission rate and a disease-free survival rate at five years of 42%.[57] Comparable results have been obtained in a number of other large trials in adults with ALL using a variety of consolidation programs.[10,59,96] High-dose cytarabine or methotrexate has been used in recent postinduction regimens; although these regimens may result in improved outcomes for certain high-risk subsets of adults, the results need to be confirmed in larger groups of patients.[95]

The treatment of patients with Ph-positive ALL remains a difficult problem. With intensified induction regimens, complete remission rates of 70% can be obtained in these patients.[58] The three-year disease-free survival rate in one study, however, was 8% for *BCR-abl*–positive patients compared with 59% for *BCR-abl*–negative patients.[95] High-dose cytarabine in consolidation may prove beneficial.[95] A small number of patients has been successfully maintained with interferon alfa.[97]

After the completion of consolidation therapy, most patients receive standard continuation chemotherapy with relatively low doses of oral methotrexate and mercaptopurine until two to three years after obtaining complete remission. Although considerable evidence supports the use of maintenance chemotherapy in children, the efficacy of this approach in adults is not as clear.[98] It is likely that most adults with standard early pre–B-cell or T-cell ALL benefit from some form of maintenance therapy; conversely, maintenance does not seem to play an important role in the current management of patients with Burkitt's B-cell ALL or Ph-positive ALL.

Relapsed and resistant leukemia. Second remissions can be achieved in about 50% of adults who relapse, either with the same drugs that were used to induce the initial remission or with alternative combinations of chemotherapy.[99] Second remissions are more commonly obtained in adults who relapse after the completion of maintenance chemotherapy than in those who relapse while still receiving chemotherapy.

A number of alternative chemotherapeutic regimens have been studied in resistant ALL, that is, in patients who fail to achieve remission with standard induction chemotherapy. Moderate to high doses of methotrexate—given incrementally from a starting dose of 200 mg per m^2 to as much as 6 grams followed by rescue with leucovorin calcium (folinic acid)—with or without asparaginase have been reported to achieve response rates of 33% to 75% in patients with resistant ALL.[100,101] Adults tolerate this regimen poorly and experience considerable gastrointestinal and hematologic toxic reactions, especially with the asparaginase combination. Administering amsacrine plus high-dose cytarabine has been reported to achieve a complete remission in 27 of 36 (75%) adults with relapsed ALL and in 2 of 4 adults with resistant leukemia.[102] A regimen of mitoxantrone plus high-dose cytarabine produced a complete remission rate of 38% (13/34) in adults with refractory ALL.[103] The use of a combination of prednisone, intermediate-dose cytarabine, mitoxantrone, and etoposide (PAME) has been shown to achieve a complete remission in 30 of 43 (70%) adult patients with relapsed or resistant ALL.[104] The prognosis of relapsed or refractory ALL is grim, however, with the median remission duration after salvage treatment of less than six months and a three-year disease-free survival rate of less than 5% to 10%.[21]

Long-term sequelae of treatment. Long-term sequelae of multiagent chemotherapy in adults with ALL have recently been assessed now that prolonged survival following therapy has become a reality for many patients. Intensive chemotherapy results in transient azoospermia in almost all men; spermatogenesis appears to recover in most patients, however, after the completion of consolidation therapy.[105] Male endocrine gonadal function does not appear to be impaired after the administration of intensive combination chemotherapy for ALL. In female patients with ALL, neither reproductive nor gonadal endocrine functions appear to be impaired following chemotherapy.[105] As in children, an increased incidence of acute myelogenous leukemia associated with chromosomal translocations involving 11q23 has been reported in adults who received prolonged exposure to epipodophyllotoxins for the treatment of ALL.[106] Avascular necrosis of bone has also been reported in adults with ALL, which may be related to the administration of combination chemotherapy regimens that include high doses of corticosteroids.[107]

Bone Marrow Transplantation

Allogeneic marrow transplantation. Allogeneic marrow transplantation, usually performed with marrow donated from an HLA-identical sibling, is an effective strategy in the treatment of adults with ALL.[108] Because of higher-dose intensity of the preparative regimen and the probable antileukemic effect mediated by the graft-versus-leukemia phenomenon, ALL patients treated with allogeneic transplantation generally have lower rates of relapse than comparable groups of patients receiving intensive combination chemotherapy.[109] Allogeneic transplantation, however, is associated with considerable morbidity and mortality as a consequence of immunosuppression, graft-versus-host disease, opportunistic infections, and toxicity from the preparative regimens.[110] Patients older than 60 years are generally not considered candidates for allogeneic transplantation. Given the small family sizes in North America, only about 30% of otherwise eligible patients in the United States have HLA-compatible sibling donors.[111]

Transplantations for advanced ALL in relapse result in a 10% to 20% long-term disease-free survival.[108] These results are superior to those for chemotherapy, but clearly the procedure benefits only a small number of patients. The disease-free survival rate for patients with ALL in second remission at three to five years following allogeneic transplantation is 32% to 52% (average, 36%); this outcome is also clearly superior to that achieved with chemotherapy, which has a disease-free survival rate at three years of only about 5% to 10%.[108,112-115] Although no randomized prospective trials have directly compared the two strategies in adults with ALL, it is likely that patients younger than 60 in second remission with a suitable donor will benefit from allogeneic transplantation, regardless of the duration of their first remission.

The treatment strategy for adults with ALL in first remission is more controversial. Data from the International Bone Marrow Transplant Registry, the European Bone Marrow Transplantation Group, and a number of additional transplantation centers indicate a 43% to 71% (average, 50%) disease-free survival rate two or more years following allogeneic marrow transplantation for adults in first complete remission.[59,108,114,116-119] Many of these patients have had one or more high-risk features, including a leukocyte count of greater than 25×10^9 per liter, older than 30 years, chromosomal translocations, or a requirement for prolonged therapy to achieve remission.

In a high-risk subgroup, patients with Ph-positive ALL, allogeneic marrow transplantation for a patient in first complete remission appears superior to administering chemotherapy alone, which has a disease-free survival rate of less than 10%. In one study, the disease-free survival rate at two years was 38% when 33 patients had transplantation during their first complete remission, 41% when transplantation was done during relapse, and 25% in refractory patients.[120]

A retrospective comparison of chemotherapy recipients and recipients of HLA-identical sibling allogeneic transplants for ALL in first remission was performed by the International Bone Marrow Transplant Registry.[109] Chemotherapy recipients were treated in 44 German hospitals according to an intensive regimen previously reported.[51] After statistical adjustments for differences in prognostic variables and time to treatment, survival was similar in the two cohorts: the five-year disease-free survival rate was 38% with chemotherapy and 44% after transplantation. Although these results were not statistically significant, patients receiving transplants had an unusually high transplantation-related mortality of 39%. Factors predicting relapse appeared to be similar for both groups of patients. No specific prognostic subgroup had an improved survival with one treatment compared with the other. In a prospective study of postremission therapy in 436 adult ALL patients achieving first remission, allogeneic transplantation resulted in a three-year disease-free survival rate of 43%.[59] This result was not significantly different from that achieved for 95 patients who received an autologous transplant (39% disease-free survival) or 96 patients who received chemotherapy (32% disease-free survival). More large prospective trials will be required to resolve the issue of optimal therapy for varying subsets of adults with ALL in first remission. Allogeneic marrow transplantation may also be useful in some ALL patients who never achieve remission even with intensive chemotherapy. In a series of 38 such patients, the disease-free survival rate at three years was 23% (37% in patients younger than 30).[121]

Transplants from HLA-identical sibling donors are available in only a few patients with ALL. Matched-unrelated donor transplantation has been done in ALL patients at various stages of disease.[122] These transplants are associated with increased morbidity and mortality from graft-versus-host disease. Currently, the role of matched-unrelated donor transplantation in the treatment of ALL remains undefined.

Autologous marrow transplantation. Autologous marrow can be harvested from ALL patients during remission, then reinfused following preparative treatment with high-dose chemotherapy with or without irradiation. Although this procedure avoids the risks of graft-versus-host disease and the need for prolonged immunosuppression, autologous transplants are associated with much higher relapse rates compared with allogeneic transplants. This is probably due to contamination of transplanted marrow with residual leukemic cells and a lack of a graft-versus-leukemia effect from an allogeneic graft.

The harvested marrow is often treated before cryopreservation in an attempt to purge the specimen of residual leukemic cells. A number of methods have been used to purge ALL remission bone marrow, including administering monoclonal antibodies directed against B-cell or T-cell differentiation antigens, mafosfamide, etoposide, and perfosfamide (4-hydroperoxycyclophosphamide).[123-126] It is not clear which if any of these procedures is effective in eradicating minimal residual leukemia.

Adults who have received an autologous transplant in second remission have disease-free survival rates ranging from 15% to 29% (average, 23%) at three years.[112,125,127-129] These results are superior to those achieved with chemotherapy alone. Again, no randomized trials have been done that directly compare these two strategies. Many patients salvaged in first relapse are not candidates for an autologous transplantation due to age, poor performance status, or organ dysfunction. Selection bias makes it difficult to directly compare autologous transplantation results with historical controls treated with chemotherapy. Nonetheless, given the poor long-term prognosis of adults who receive chemotherapy after a first relapse, it is reasonable to consider patients in their second complete remission without an HLA-matched donor as candidates for an autologous transplant. Autologous transplantations ideally should be performed as soon as possible after achieving a second remission.

In early studies, disease-free survival in adults in first remission following autologous transplantation appeared promising, with rates of 32% to 65% (average, 41%).[119,123,124,127,128] Prospective trials to date, however, demonstrate no advantage of consolidation treatment with an autologous transplant over chemotherapy. In the French Group trial, patients without an allogeneic donor were randomly assigned to receive autologous transplantation or intensification with chemotherapy. The disease-free survival rate based on intention-to-treat analysis for 95 patients receiving an autologous transplant was 39%, and that for 96 patients receiving chemotherapy was 32%; this difference was not significant.[59] For the 63 patients who actually received an autologous transplant in their first remission, the three-year disease-free survival rate was 51%. It appears premature at this time to recommend autologous marrow transplantation for adults with ALL in first complete remission. It is likely that improved conditioning regimens, more effective methods for eradicating marrow residual disease ex vivo, and immunomodulation after transplantation will make autologous transplantation a more promising procedure for high-risk adults with ALL in first remission. The treatment results for adults with ALL following either chemotherapy or allogeneic or autologous transplantation are summarized in Table 5.* Recommendations for managing adults with ALL in first remission are given in Table 6.[130,131]

*References 5, 9, 57-59, 65-67, 95, 96, 112-119, 123-125, and 127-129.

TABLE 5.—*Treatment of Adult Acute Lymphoblastic Leukemia (ALL) With Chemotherapy and Allogeneic or Autologous Bone Marrow Transplantation*

Treatment	Probability of Disease-Free Survival at 3-5 Yr, %	
	1st Complete Remission	2nd Complete Remission
Chemotherapy		
T cell	45-60*	5-10
CALLA-positive, early pre-B cell	30-35*	5-10
CALLA-negative, early pre-B cell	20-25*	5-10
B cell	10-60†	5-10
Ph-positive ALL	<10‡	5-10
Allogeneic transplant	50§ (43-71)‖	36§ (32-52)¶
Autologous transplant	41§ (32-65)#	23§ (15-29)**

CALLA = common ALL antigen, Ph = Philadelphia chromosome

*From Gaynor et al,[5] Hussein et al,[9] Linker et al,[57] and Kantarjian et al.[96]

†From Gill et al,[65] Fenaux et al,[66] and Pees et al.[67]

‡From Linker et al,[57] Westbrook et al,[58] and Hoelzer.[95]

§Weighted average = Σ disease-free survival × No. of patients in the study ÷ total No. of patients.

‖From Fière et al,[59] Gratwohl et al,[114] Vernant et al,[116] Chao et al,[117] Mrsic et al,[118] and Blaise et al.[119] N = 514.

¶ From Arcese et al,[112] Weyman et al,[113] Gratwohl et al,[114] and Blume et al.[115] N = 467.

#From Fière et al,[59] Blaise et al,[119] Simonsson et al,[123] Gilmore et al,[124] Gorin et al,[127] and Rizzoli et al.[128] N = 435.

**From Arcese et al,[112] Soiffer et al,[125] Gorin et al,[127] Rizzoli et al,[128] and Doney et al.[129] N = 185.

Peripheral blood stem-cell transplantation. Peripheral blood stem cells can be harvested from patients in remission using leukapheresis after stimulating with cytotoxic chemotherapy and recombinant growth factors. Studies have shown that the number of hematopoietic progenitors harvested with this method can exceed those obtained with a bone marrow harvest.[132] These "mobilized" stem cells are then used to reconstitute the marrow in patients treated with marrow ablative chemotherapy.[133] Recent data suggest that preferential harvesting of *BCR-abl*–negative peripheral stem cells may be possible during early recovery from chemotherapy-induced hypoplasia in chronic myeloid leukemia.[134] This technology may possibly be used as a "purging" technique in the treatment of patients with Ph- positive ALL and other subtypes of ALL with identifiable cytogenetic or molecular markers.[135]

Conclusions

The immunophenotypic and molecular characterization of lymphoblasts in ALL has provided important insights into the nature of leukemogenesis. Advances in the understanding of the disease have resulted in improved methods of diagnosis, more accurate prognostic criteria, and more sensitive means for detecting minimal residual disease. Intensive combination chemotherapy and bone marrow transplantation now offer the possibility of cure for a substantial number of adults. Future investigation will need to more precisely define the indications for chemotherapy versus allogeneic, autologous, or peripheral stem-cell transplantation in the treatment of ALL. Specific treatment regimens will need to be more clearly and individually defined for different disease subsets. It is probable that further characterization of the disordered gene regulation found in ALL lymphoblasts will lead to an improved understanding of the disease's pathogenesis. Furthermore, a better understanding of the genetic basis of ALL may allow the implementation of novel therapies targeted at the underlying molecular or biochemical abnormalities found within the lymphoblast.

REFERENCES

1. Bennett JM, Catovsky D, Daniel MT, et al: Proposals for the classification of the acute leukaemias—French-American-British (FAB) co-operative group. Br J Haematol 1976; 33:451-458

2. Foa R, Migone N, Saitta M, et al: Different stages of B cell differentiation in non-T acute lymphoblastic leukemia. J Clin Invest 1984; 74:1756-1763

3. Waldmann TA: The arrangement of immunoglobulin and T cell receptor genes in human lymphoproliferative disorders. Adv Immunol 1987; 40:247-321 (350 ref)

4. Jongeneel CV, Quackenbush EJ, Ronco P, Verroust P, Carrel S, Letarte M: Common acute lymphoblastic leukemia antigen expressed on leukemia and melanoma cell lines has neutral endopeptidase activity. J Clin Invest 1989; 83:713-717

5. Gaynor J, Chapman D, Little C, et al: A cause-specific hazard rate analysis of prognostic factors among 199 adults with acute lymphoblastic leukemia: The Memorial Hospital experience since 1969. J Clin Oncol 1988; 6:1014-1030 [erratum published in J Clin Oncol 1988; 6:1522]

6. Radford JE Jr, Burns CP, Jones MP, et al: Adult acute lymphoblastic leukemia: Results of the Iowa HOP-L protocol. J Clin Oncol 1989; 7:58-66

7. Linker CA, Levitt LJ, O'Donnell M, et al: Improved results of treatment of adult acute lymphoblastic leukemia. Blood 1987; 69:1242-1248

8. Gingrich RD, Burns CP, Armitage JO, et al: Long-term relapse-free survival in adult acute lymphoblastic leukemia. Cancer Treat Rep 1985; 69:153-160

TABLE 6.—*Adults With Acute Lymphoblastic Leukemia (ALL) in First Complete Remission—Recommendations for Treatment*

ALL Subtype	Recommendations
T cell	Aggressive postremission chemotherapy; no allogeneic transplant unless relapse. For patients without HLA-matched sibling donors, consider cryopreserving remission marrow or peripheral blood progenitor cells to use in case of relapse
B cell	Chemotherapy using high doses of cyclophosphamide and methotrexate in combination with an anthracycline, cytarabine, and teniposide; no allogeneic transplantation unless relapse. For patients without HLA-matched sibling donors, consider cryopreserving remission marrow or peripheral blood progenitor cells for use in case of relapse
Early pre-B cell	Allogeneic transplantation in first CR for patients who have chromosomal translocations—other than t(8;14)(q24;q32)—or who require more than 4-5 wk to enter CR. Aggressive postremission chemotherapy for rest of patients and allogeneic transplantation if relapse occurs and HLA-matched sibling donor available. Consider cryopreserving first remission marrow or peripheral blood progenitor cells if no allogeneic donor available
Ph-positive	Allogeneic transplantation in first CR; if no allogeneic donor available, consider high-dose cytarabine for consolidation followed by interferon alfa; or entry into phase I-II trials (for example, therapy targeting the fusion gene product by engineered ribozymes or antisense oligomeres)*

CR = complete remission, HLA = human leukocyte antigen, Ph = Philadelphia chromosome

*From Shore et al[130] and Skórski et al.[131]

9. Hussein KK, Dahlberg S, Head D, et al: Treatment of acute lymphoblastic leukemia in adults with intensive induction, consolidation, and maintenance chemotherapy. Blood 1989; 73:57-63

10. Thiel E, Kranz BR, Raghavachar A, et al: Prethymic phenotype and genotype of pre-T (CD7+/ER−)-cell leukemia and its clinical significance within adult acute lymphoblastic leukemia. Blood 1989; 73:1247-1258

11. First MIC Cooperative Study Group: Morphologic, immunologic, and cytogenetic (MIC) working classification of acute lymphoblastic leukemias—Report of the workshop held in Leuven, Belgium, April 22-23, 1985. Cancer Genet Cytogenet 1986; 23:189-197

12. Kitchingman GR, Rovigatti U, Mauer AM, Melvin S, Murphy SB, Stass S: Rearrangement of immunoglobulin heavy chain genes in T cell acute lymphoblastic leukemia. Blood 1985; 65:725-729

13. Nourse J, Mellentin JD, Galili N, et al: Chromosomal translocation t(1;19) results in synthesis of a homeobox fusion mRNA that codes for a potential chimeric transcription factor. Cell 1990; 60:535-545

14. Kamps MP, Murre C, Sun XH, Baltimore D: A new homeobox gene contributes the DNA binding domain of the t(1;19) translocation protein in pre-B ALL. Cell 1990; 60:547-555

15. Bouffet E, Frappaz D, Pinkerton R, Favrot M, Philip T: Burkitt's lymphoma: A model for clinical oncology. Eur J Cancer 1991; 27:504-509

16. Gale RP, Ben Bassat I: Hybrid acute leukaemia. Br J Haematol 1987; 65:261-264

17. Drexler HG, Thiel E, Ludwig WD: Review of the incidence and clinical relevance of myeloid antigen-positive acute lymphoblastic leukemia. Leukemia 1991; 5:637-645

18. Vaickus L, Ball ED, Foon KA: Immune markers in hematologic malignancies. Crit Rev Oncol Hematol 1991; 11:267-297

19. Bloomfield CD, Secker-Walker LM, Goldman AI, et al: Six-year follow-up of the clinical significance of karyotype in acute lymphoblastic leukemia. Cancer Genet Cytogenet 1989; 40:171-185

20. Williams DL, Raimondi S, Rivera G, George S, Berard CW, Murphy SB: Presence of clonal chromosome abnormalities in virtually all cases of acute lymphoblastic leukemia (Letter). N Engl J Med 1985; 313:640-641

21. Hoelzer D: Acute lymphoblastic leukemia in adults, *In* Hoffman R, Benz E, Shattil S, Furie B, Cohen H (Eds): Hematology: Basic Principles and Practice. New York, NY, Churchill Livingstone, 1991, pp 793-804

22. Hagemeijer A, van der Plas DC: Clinical relevance of cytogenetics in acute leukemia. Hamatol Bluttransfus 1990; 33:23-30

23. Kurzrock R, Gutterman JU, Talpaz M: The molecular genetics of Philadelphia chromosome-positive leukemias. N Engl J Med 1988; 319:990-998

24. Konopka JB, Watanabe SM, Witte ON: An alteration of the human c-*abl* protein in K562 leukemia cells unmasks associated tyrosine kinase activity. Cell 1984; 37:1035-1042

25. Kurzrock R, Shtalrid M, Romero P, et al: A novel c-*abl* protein product in Philadelphia-positive acute lymphoblastic leukaemia. Nature 1987; 325: 631-635

26. Daley GQ, Van Etten RA, Baltimore D: Induction of chronic myelogenous leukemia in mice by the P210 *bcr/abl* gene of the Philadelphia chromosome. Science 1990; 247:824-830

27. Heisterkamp N, Jenster G, ten Hoeve J, Zovich D, Pattengale PK, Groffen J: Acute leukaemia in *bcr/abl* transgenic mice. Nature 1990; 344: 251-253

28. Maurer J, Janssen JW, Thiel E, et al: Detection of chimeric BCR-ABL genes in acute lymphoblastic leukaemia by the polymerase chain reaction. Lancet 1991; 337:1055-1058

29. Klein G: Specific chromosomal translocations and the genesis of B-cell–derived tumors in mice and men. Cell 1983; 32:311-315

30. Taub R, Kelly K, Battey J, et al: A novel alteration in the structure of an activated c-*myc* gene in a variant t(2;8) Burkitt lymphoma. Cell 1984; 37: 511-520

31. Adams JM, Gerondakis S, Webb E, Corcoran LM, Cory S: Cellular *myc* oncogene is altered by chromosome translocation to an immunoglobulin locus in murine plasmacytomas and is rearranged similarly in human Burkitt lymphomas. Proc Natl Acad Sci USA 1983; 80:1982-1986

32. Adams JM, Harris AW, Pinkert CA, et al: The c-*myc* oncogene driven by immunoglobulin enhancers induces lymphoid malignancy in transgenic mice. Nature 1985; 318:533-538

33. Lombardi L, Newcomb EW, Dalla-Favera R: Pathogenesis of Burkitt lymphoma: Expression of an activated c-*myc* oncogene causes the tumorigenic conversion of EBV-infected human B lymphoblasts. Cell 1987; 49:161-170

34. Mirro J, Kitchingman G, Williams D, et al: Clinical and laboratory characteristics of acute leukemia with the 4;11 translocation. Blood 1986; 67: 689-697

35. Stong RC, Korsmeyer SJ, Parkin JL, Arthur DC, Kersey JH: Human acute leukemia cell line with the t(4;11) chromosomal rearrangement exhibits B lineage and monocytic characteristics. Blood 1985; 65:21-31

36. Huret JL, Brizard A, Slater R, et al: Cytogenetic heterogeneity in t(11;19) acute leukemia: Clinical, hematological and cytogenetic analyses of 48 patients—Updated published cases and 16 new observations. Leukemia 1993; 7:152-160

37. Diaz MO, Le Beau MM, Pitha P, Rowley JD: Interferon and c-*ets*-1 genes in the translocation (9;11)(p22;q23) in human acute monocytic leukemia. Science 1986; 231:265-267

38. Abe R, Sandberg AA: Significance of abnormalities involving chromosomal segment 11q22-25 in acute leukemia. Cancer Genet Cytogenet 1984; 13:121-127

39. Pui CH, Behm FG, Raimondi SC, et al: Secondary acute myeloid leukemia in children treated for acute lymphoid leukemia. N Engl J Med 1989; 321:136-142

40. Thirman MJ, Gill HJ, Burnett RC, et al: Rearrangement of the *MLL* gene in acute lymphoblastic and acute myeloid leukemias with 11q23 chromosomal translocations. N Engl J Med 1993; 329:909-914

41. Carroll AJ, Crist WM, Parmley RT, Roper M, Cooper MD, Finley WH: Pre-B cell leukemia associated with chromosome translocation 1;19. Blood 1984; 63:721-724

42. Dedera D, Waller E, LeBrun DP, et al: Chimeric homeobox gene *E2A-PBX1* induces proliferation, apoptosis, and malignant lymphomas in transgenic mice. Cell 1993; 74:833-843

43. Croce CM, Isobe M, Palumbo A, et al: Gene for α-chain of human T-cell receptor: Location on chromosome 14 region involved in T-cell neoplasms. Science 1985; 227:1044-1047

44. Mellentin JD, Smith SD, Cleary ML: *lyl-1*, a novel gene altered by chromosomal translocation in T cell leukemia, codes for a protein with a helix-loop-helix DNA binding motif. Cell 1989; 58:77-83

45. McGuire EA, Hockett RD, Pollock KM, Bartholdi MF, O'Brien SJ, Korsmeyer SJ: The t(11;14)(p15;q11) in a T-cell acute lymphoblastic leukemia cell line activates multiple transcripts, including *Ttg-1*, a gene encoding a potential zinc finger protein. Mol Cell Biol 1989; 9:2124-2132

46. Kagan J, Finger LR, Letofsky J, Finan J, Nowell PC, Croce CM: Clustering of breakpoints on chromosome 10 in acute T-cell leukemias with the t(10;14) chromosome translocation. Proc Natl Acad Sci USA 1989; 86: 4161-4165

47. Chen Q, Cheng JT, Tasi LH, et al: The *tal* gene undergoes chromosome translocation in T cell leukemia and potentially encodes a helix-loop-helix protein. EMBO J 1990; 9:415-424

48. Reynolds TC, Smith SD, Sklar J: Analysis of DNA surrounding the breakpoints of chromosomal translocations involving the β T cell receptor gene in human lymphoblastic neoplasms. Cell 1987; 50:107-117

49. Denny CT, Yoshikai Y, Mak TW, Smith SD, Hollis GF, Kirsch IR: A chromosome 14 inversion in a T-cell lymphoma is caused by site-specific recombination between immunoglobulin and T-cell receptor loci. Nature 1986; 320:549-551

50. Rossi JF, Bataille R, Chappard D, Alexandre C, Janbon C: B cell malignancies presenting with unusual bone involvement and mimicking multiple myeloma—Study of nine cases. Am J Med 1987; 83:10-16

51. Hoelzer D, Thiel E, Löffler H, et al: Prognostic factors in a multicenter study for treatment of acute lymphoblastic leukemia in adults. Blood 1988; 71:123-131

52. Sarris AH, Kempin S, Berman E, et al: High incidence of disseminated intravascular coagulation during remission induction of adult patients with acute lymphoblastic leukemia. Blood 1992; 79:1305-1310

53. Bachhuber R, Fitchen JH, Harty-Golder B: Rash and eosinophilia in a 23-year-old man—Oregon Health Sciences University (Clinicopathologic Conference). West J Med 1982; 137:221-227

54. Niebrugge DJ, Benjamin DR: Bone marrow necrosis preceding acute lymphoblastic leukemia in childhood. Cancer 1983; 52:2162-2164

55. Lensink DB, Barton A, Appelbaum FR, Hammond WP 4th: Cyclic neutropenia as a premalignant manifestation of acute lymphoblastic leukemia. Am J Hematol 1986; 22:9-16

56. Cohen LF, Balow JE, Magrath IT, Poplack DG, Ziegler JL: Acute tumor lysis syndrome—A review of 37 patients with Burkitt's lymphoma. Am J Med 1980; 68:486-491

57. Linker CA, Levitt LJ, O'Donnell M, Forman SJ, Ries CA: Treatment of adult acute lymphoblastic leukemia with intensive cyclical chemotherapy: A follow-up report. Blood 1991; 78:2814-2822

58. Westbrook CA, Hooberman AL, Spino C, et al: Clinical significance of the *BCR-ABL* fusion gene in adult acute lymphoblastic leukemia: A Cancer and Leukemia Group B Study (8762). Blood 1992; 80:2983-2990

59. Fière D, Lepage E, Sebban C, et al: Adult acute lymphoblastic leukemia: A multicentric randomized trial testing bone marrow transplantation as post-remission therapy—The French Group on Therapy for Adult Acute Lymphoblastic Leukemia. J Clin Oncol 1993; 11:1990-2001

60. Barnett MJ, Greaves MF, Amess JA, et al: Treatment of acute lymphoblastic leukaemia in adults. Br J Haematol 1986; 64:455-468

61. Henderson ES, Scharlau C, Cooper MR, et al: Combination chemotherapy and radiotherapy for acute lymphocytic leukemia in adults: Results of CALGB protocol 7113. Leuk Res 1979; 3:395-407

62. Taylor PR, Reid MM, Bown N, Hamilton PJ, Proctor SJ: Acute lymphoblastic leukemia in patients aged 60 years and over: A population-based study of incidence and outcome. Blood 1992; 80:1813-1817

63. Sobol RE, Mick R, Royston I, et al: Clinical importance of myeloid antigen expression in adult acute lymphoblastic leukemia. N Engl J Med 1987; 316:1111-1117

64. Plunkett W, Liliemark JO, Estey E, Keating MJ: Saturation of ara-CTP accumulation during high-dose ara-C therapy: Pharmacologic rationale for intermediate-dose ara-C. Semin Oncol 1987; 14(suppl 1):159-166

65. Gill PS, Meyer PR, Pavlova Z, Levine AM: B cell acute lymphocytic leukemia in adults—Clinical, morphologic, and immunologic findings. J Clin Oncol 1986; 4:737-743

66. Fenaux P, Lai JL, Miaux O, Zandecki M, Jouet JP, Bauters F: Burkitt cell acute leukaemia (L3 ALL) in adults: A report of 18 cases. Br J Haematol 1989; 71:371-376

67. Pees HW, Radtke H, Schwamborn J, Graf N: The BFM-protocol for HIV-negative Burkitt's lymphomas and L3 ALL in adult patients: A high chance for cure. Ann Hematol 1992; 65:201-205

68. McMaster ML, Greer JP, Greco FA, Johnson DH, Wolff SN, Hainsworth JD: Effective treatment of small-noncleaved-cell lymphoma with high-intensity, brief-duration chemotherapy. J Clin Oncol 1991; 9:941-946

69. Urbano-Ispizua A, Matutes E, Villamor N, et al: Clinical significance of the presence of myeloid associated antigens in acute lymphoblastic leukaemia. Br J Haematol 1990; 75:202-207

70. Guyotat D, Campos L, Shi ZH, et al: Myeloid surface antigen expression in adult acute lymphoblastic leukemia. Leukemia 1990; 4:664-666

71. Childs CC, Hirsch-Ginsberg C, Walters RS, et al: Myeloid surface antigen-positive acute lymphoblastic leukemia (My+ ALL): Immunophenotypic, ultrastructural, cytogenetic, and molecular characteristics. Leukemia 1989; 3:777-783

72. Preti A, Huh Y, O'Brien S, et al: Prognostic significance of positive myeloid markers in adult ALL (Abstr). Blood 1993; 82:57a

73. Hirsch-Ginsberg C, Huh YO, Kagan J, Liang JC, Stass SA: Advances in the diagnosis of acute leukemia. Hematol Oncol Clin North Am 1993; 7:1-46

74. Zehnbauer BA, Pardoll DM, Burke PJ, Graham ML, Vogelstein B: Immunoglobulin gene rearrangements in remission bone marrow specimens from patients with acute lymphoblastic leukemia. Blood 1986; 67:835-838

75. Miyamura K, Tanimoto M, Morishima Y, et al: Detection of Philadelphia chromosome-positive acute lymphoblastic leukemia by polymerase chain reaction: Possible eradication of minimal residual disease by marrow transplantation. Blood 1992; 79:1366-1370

76. Hughes TP, Morgan GJ, Martiat P, Goldman JM: Detection of residual leukemia after bone marrow transplant for chronic myeloid leukemia: Role of polymerase chain reaction in predicting relapse. Blood 1991; 77:874-878

77. Yamada M, Hudson S, Tournay O, et al: Detection of minimal disease in hematopoietic malignancies of the B-cell lineage by using third-complementarity-determining region (CDR-III)-specific probes. Proc Natl Acad Sci USA 1989; 86:5123-5127

78. Brisco MJ, Condon J, Hughes E, et al: Outcome prediction in childhood acute lymphoblastic leukaemia by molecular quantification of residual disease at the end of induction. Lancet 1994; 343:196-200

79. Kneba M, Bolz I, Linke B, Bertram J, Rothaupt D, Hiddemann W: Characterization of clone-specific rearranged T-cell receptor γ-chain genes in lymphomas and leukemias by the polymerase chain reaction and DNA sequencing. Blood 1994; 84:574-581

80. Hess CE, Zirkle JW: Results of induction therapy with vincristine and prednisone alone in adult acute lymphoblastic leukemia: Report of 43 patients and review of the literature. Am J Hematol 1982; 13:63-71

81. Willemze R, Hillen H, Hartgrink-Groeneveld CA, Haanen C: Treatment of acute lymphoblastic leukemia in adolescents and adults: A retrospective study of 41 patients (1970-1973). Blood 1975; 46:823-834

82. Gottlieb AJ, Weinberg V, Ellison RR, et al: Efficacy of daunorubicin in the therapy of adult acute lymphocytic leukemia: A prospective randomized trial by cancer and leukemia group B. Blood 1984; 64:267-274

83. Rohatiner AZ, Bassan R, Battista R, et al: Intensive chemotherapy for acute lymphoblastic leukaemia in adults. Hamatol Bluttransfus 1990; 33: 413-418

84. Arlin Z, Feldman E, Ahmed T, et al: After 25 years with vincristine/prednisone, have we found a better induction therapy for ALL? (Abstr) Blood 1991; 78:447a

85. Kasparu H, Sreter L, Holowiecki J, et al: Intensified induction therapy for ALL in adults: A multicenter trial. Onkologie 1991; 14(suppl 1):80

86. Kantarjian HM, Walters RS, Smith TL, et al: Identification of risk groups for development of central nervous system leukemia in adults with acute lymphocytic leukemia. Blood 1988; 72:1784-1789

87. Bleyer WA, Poplack DG: Prophylaxis and treatment of leukemia in the central nervous system and other sanctuaries. Semin Oncol 1985; 12:131-148

88. Bleyer WA, Poplack DG: Intraventricular versus intralumbar methotrexate for central-nervous-system leukemia: Prolonged remission with the Ommaya reservoir. Med Pediatr Oncol 1979; 6:207-213

89. Omura GA, Moffitt S, Vogler WR, Salter MM: Combination chemotherapy of adult acute lymphoblastic leukemia with randomized central nervous system prophylaxis. Blood 1980; 55:199-204

90. Bleyer WA: CNS Leukemia, *In* Henderson ES, Lister TA (Eds): Leukemia, 5th edition. Philadelphia, Pa, WB Saunders, 1990, pp 733-768

91. Tucker J, Prior PF, Green CR, et al: Minimal neuropsychological sequelae following prophylactic treatment of the central nervous system in adult leukaemia and lymphoma. Br J Cancer 1989; 60:775-780

92. Fière D, Extra JM, David B, et al: Treatment of 218 adult acute lymphoblastic leukemias. Semin Oncol 1987; 14(suppl 1):64-66

93. Stryckmans P, De Witte T, Bitar N, et al: Cytosine arabinoside for induction, salvage, and consolidation therapy of adult acute lymphoblastic leukemia. Semin Oncol 1987; 14(suppl 1):67-72

94. Ellison RR, Mick R, Cuttner J, et al: The effects of postinduction intensification treatment with cytarabine and daunorubicin in adult acute lymphocytic leukemia: A prospective randomized clinical trial by Cancer and Leukemia Group B. J Clin Oncol 1991; 9:2002-2015

95. Hoelzer D: Treatment of acute lymphoblastic leukemia. Semin Hematol 1994; 31:1-15

96. Kantarjian HM, Walters RS, Keating MJ, et al: Results of the vincristine, doxorubicin, and dexamethasone regimen in adults with standard- and high-risk acute lymphocytic leukemia. J Clin Oncol 1990; 8:994-1004

97. Ohyashiki K, Ohyashiki JH, Tauchi T, et al: Treatment of Philadelphia chromosome-positive acute lymphoblastic leukemia: A pilot study which raises important questions. Leukemia 1991; 5:611-614

98. Miller DR: Acute lymphoblastic leukemia. Pediatr Clin North Am 1980; 27:269-291

99. Freund M, De Boben M, Diedrich H, et al: Treatment of relapsed acute lymphocytic leukemia in adults. Hamatol Bluttransfus 1990; 33:432-436

100. Yap BS, McCredie KB, Keating MJ, Bodey GP, Freireich EJ: Asparaginase and methotrexate combination chemotherapy in relapsed acute lymphoblastic leukemia in adults. Cancer Treat Rep 1981; 65(suppl 1):83-87

101. Peterson BA, Bloomfield CD: High-dose methotrexate for the remission induction of refractory adult acute lymphocytic leukemia. Med Pediatr Oncol 1978; 5:79-84

102. Arlin ZA, Feldman E, Kempin S, et al: Amsacrine with high-dose cytarabine is highly effective therapy for refractory and relapsed acute lymphoblastic leukemia in adults. Blood 1988; 72:433-435

103. Kantarjian HM, Estey EH, O'Brien S, et al: Intensive chemotherapy with mitoxantrone and high-dose cytosine arabinoside followed by granulocyte-macrophage colony-stimulating factor in the treatment of patients with acute lymphocytic leukemia. Blood 1992; 79:876-881

104. Milpied N, Gisselbrecht C, Harousseau JL, et al: Successful treatment of adult acute lymphoblastic leukemia after relapse with prednisone, intermediate-dose cytarabine, mitoxantrone, and etoposide (PAME) chemotherapy. Cancer 1990; 66:627-631

105. Kreuser ED, Hetzel WD, Heit W, et al: Reproductive and endocrine gonadal functions in adults following multidrug chemotherapy for acute lymphoblastic or undifferentiated leukemia. J Clin Oncol 1988; 6:588-595

106. Rugo HS, Ries CA, Levitt LJ, O'Donnell M, Foreman S, Linker C: Risk of myeloid relapse from intensive cyclical chemotherapy containing teniposide for adult ALL (Abstr). Proc Am Soc Clin Oncol 1994; 13:307

107. Chan-Lam D, Prentice A, Copplestone J: Avascular necrosis of bone following intensified steroid therapy for ALL and high-grade lymphoma. Br J Haematol 1994; 86:227-230

108. Bortin MM, Horowitz MM, Rowlings PA, et al: 1993 progress report from the International Bone Marrow Transplant Registry—Advisory Committee of the International Bone Marrow Transplant Registry. Bone Marrow Transplant 1993; 12:97-104

109. Horowitz MM, Messerer D, Hoelzer D, et al: Chemotherapy compared with bone marrow transplantation for adults with acute lymphoblastic leukemia in first remission. Ann Intern Med 1991; 115:13-18

110. Sutton L, Kuentz M, Cordonnier C, et al: Allogeneic bone marrow transplantation for adult acute lymphoblastic leukemia in first complete remission: Factors predictive of transplant-related mortality and influence of total body irradiation modalities. Bone Marrow Transplant 1993; 12:583-589

111. Beatty PG, Hansen JA, Longton GM, et al: Marrow transplantation from HLA-matched unrelated donors for treatment of hematologic malignancies. Transplantation 1991; 51:443-447

112. Arcese W, Amadori S, Meloni G, et al: Allogeneic or Autologous Bone Marrow Transplantation for Intensification of Salvage Therapy in Patients with High-Risk Advanced Acute Lymphoblastic Leukemia. Semin Hematol 1991; 28:116-121

113. Weyman C, Graham-Pole J, Emerson S, et al: Use of cytosine arabinoside and total body irradiation as conditioning for allogeneic marrow transplantation in patients with acute lymphoblastic leukemia: A multicenter survey. Bone Marrow Transplant 1993; 11:43-50

114. Gratwohl A, Hermans J, Zwaan F: BMT for ALL in Europe, *In* Gale R, Hoelzer D (Eds): Acute Lymphoblastic Leukemia. New York, NY, Wiley-Liss, 1990, pp 271-278

115. Blume KG, Schmidt GM, Chao NJ, Forman SJ: Bone marrow transplantation from histocompatible sibling donors for patients with acute lymphoblastic leukemia. Hamatol Bluttransfus 1990; 33:636-637

116. Vernant JP, Marit G, Maraninchi D, et al: Allogeneic bone marrow transplantation in adults with acute lymphoblastic leukemia in first complete remission. J Clin Oncol 1988; 6:227-231

117. Chao NJ, Forman SJ, Schmidt GM, et al: Allogeneic bone marrow transplantation for high-risk acute lymphoblastic leukemia during first complete remission. Blood 1991; 78:1923-1927

118. Mrsic M, Nemet D, Labar B, et al: Chemotherapy versus allogeneic bone marrow transplantation in adults with acute lymphoblastic leukemia. Transplant Proc 1993; 25:1268-1270

119. Blaise D, Gaspard MH, Stoppa AM, et al: Allogeneic or autologous bone marrow transplantation for acute lymphoblastic leukemia in first complete remission. Bone Marrow Transplant 1990; 5:7-12

120. Barrett AJ, Horowitz MM, Ash RC, et al: Bone marrow transplantation for Philadelphia chromosome-positive acute lymphoblastic leukemia. Blood 1992; 79:3067-3070

121. Biggs JC, Horowitz MM, Gale RP, et al: Bone marrow transplants may cure patients with acute leukemia never achieving remission with chemotherapy. Blood 1992; 80:1090-1093

122. Busca A, Anasetti C, Anderson G, et al: Unrelated donor or autologous marrow transplantation for treatment of acute leukemia. Blood 1994; 83: 3077-3084

123. Simonsson B, Burnett AK, Prentice HG, et al: Autologous bone marrow transplantation with monoclonal antibody purged marrow for high risk acute lymphoblastic leukemia. Leukemia 1989; 3:631-636

124. Gilmore MJ, Hamon MD, Prentice HG, et al: Failure of purged autologous bone marrow transplantation in high risk acute lymphoblastic leukaemia in first complete remission. Bone Marrow Transplant 1991; 8:19-26

125. Soiffer RJ, Roy DC, Gonin R, et al: Monoclonal antibody-purged autologous bone marrow transplantation in adults with acute lymphoblastic leukemia at high risk of relapse. Bone Marrow Transplant 1993; 12:243-251

126. Auber ML, Horwitz LJ, Blaauw A, et al: Evaluation of drugs for elimination of leukemic cells from the bone marrow of patients with acute leukemia. Blood 1988; 71:166-172

127. Gorin NC, Aegerter P, Auvert B: Autologous bone marrow transplantation for acute leukemia in remission: An analysis of 1322 cases. Hamatol Bluttransfus 1990; 33:660-666

128. Rizzoli U, Mangoni L, Carella AM, et al: Drug-mediated marrow purging: Mafosfamide in adult acute leukemia in remission—The experience of the Italian study group. Bone Marrow Transplant 1989; 4(suppl 1):190-194

129. Doney K, Buckner CD, Fisher L, et al: Autologous bone marrow transplantation for acute lymphoblastic leukemia. Bone Marrow Transplant 1993; 12:315-321

130. Shore SK, Nabissa PM, Reddy EP: Ribozyme-mediated cleavage of the BCR-ABL oncogene transcript: In vitro cleavage of RNA and in vivo loss of P210 protein-kinase activity. Oncogene 1993; 8:3183-3188

131. Skórski T, Nieborowska-Skórska M, Barletta C, et al: Highly efficient elimination of Philadelphia leukemic cells by exposure to *bcr/abl* antisense oligodeoxynucleotides combined with mafosfamide. J Clin Invest 1993; 92: 194-202

132. Siena S, Bregni M, Brando B, Ravagnani F, Bonadonna G, Gianni AM: Circulation of CD34+ hematopoietic stem cells in the peripheral blood of high-dose cyclophosphamide-treated patients: Enhancement by intravenous recombinant human granulocyte-macrophage colony-stimulating factor. Blood 1989; 74:1905-1914

133. Chao NJ, Schriber JR, Grimes K, et al: Granulocyte colony-stimulating factor 'mobilized' peripheral blood progenitor cells accelerate granulocyte and platelet recovery after high-dose chemotherapy. Blood 1993; 81:2031-2035

134. Carella AM, Podesta M, Frassoni F, et al: Selective overshoot of Ph-negative blood hemopoietic cells after intensive idarubicin-containing regimen and their repopulating capacity after reinfusion. Stem Cells 1993; 3:67-72

135. Carella AM, Pollicardo N, Pungolino E, et al: Mobilization of cytogenetically 'normal' blood progenitors cells by intensive conventional chemotherapy for chronic myeloid and acute lymphoblastic leukemia. Leuk Lymphoma 1993; 9:477-483